

Traditional Uses of Essential Oils in Light of Receptor Science

Kurt Schnaubelt¹, Pacific Institute of Aromatherapy, San Rafael, USA.

presented at

2nd International Scientific Aromatherapy Symposium, March 19 - 21, 1999 in

Grasse, France

Abstract

Because of their biological and coevolutionary history, aromatic plant substances are major players in many systems of cellular biochemistry, among them the cascade of events mediating inflammation, binding to receptors in a number of systems (competitive and noncompetitive mechanisms) and interacting significantly with Calcium influx. Studies aimed at clarifying the influences of selected oil components on membrane proteins, enzymes and receptors promise to provide more detailed understanding of the phenomena of essential oil pharmacology.

Questions of Paradigm

In contemporary western industrialized cultures the areas of nutrition and health maintenance (prevention and treatment of disease) have in common that reductionist approaches, relying on (isolated) substances demonstrated to have specific activities, exist parallel to contrasting approaches, in which more wholistic or integrative principles are preferred, relying on substances provided by nature, mainly from the plant world.

A decision to favor whole foods and natural remedies over isolated substances is very difficult to support exclusively by reductionist/scientific proof. Individuals favoring these approaches generally arrive at their decisions through mental and philosophical processes. With reference to the popular phenomenon of aromatherapy the apparent gap between popular embrace of the evolving modality of essential oil therapy and the seemingly insurmountable difficulties in explaining its effects scientifically have sometimes led to fairly dogmatic statements of scientists, claiming that only scientifically provable effects could be considered real and true and that the assumptions of the

¹ Address correspondence to

Dr. Kurt Schnaubelt, Pacific Institute of Aromatherapy, POB 6723, San Rafael, CA 94903

aromatherapy users amount to not much more than old wives tales or New Age nebulousness.

The fact remains that the interactions of complex mixtures such as whole foods or essential oils are extremely difficult to assess with the reductionist method alone. These serious difficulties are almost never mentioned:

1) How is it possible to determine all the substances present in an essential oil (or a whole food) ? Modern analytical science has been able to detect and or isolate many components. We know about main components and we know about high impact trace components. We know particularly about those that promised exploitability and therefore found research funding. We do not know about substances and concepts which do not seem exploitable to those who provide the funding. Ultimately our scientific knowledge of substances is determined to an overriding degree by which classes of substances are being targeted because of the perception of financial profit in the given economic or regulatory environment (1). An example might be the current trend in the US to manufacture each and every industrialized food product sodium free. It appears that the industrial length to which this concept is taken is quite out of proportion with the potential benefits of a reduced sodium intake.

2) How do we determine quality and extent of the interactions of all the substances with the broad variety of physiological target systems with which we know they interact?

3) How do we determine the quality of the outcome? If eating whole foods or using natural therapies were truly better how would we determine that? To the contrary in instances where supplementing a substance or a number of clearly defined substances may have tangible positive results we are often able to demonstrate this. Then again how do we account for long term effects? Some attach a value to the notion of feeling well and wholesome. Others believe in progress and want to rely on the latest breakthrough in nutritional/supplement science or pharmacology.

It appears that these questions can ultimately not be answered by science alone. Any meaningful answer to these questions requires that we assign a quality to nature and our place in it. We need to decide whether nature is to be respected and whether we fare

best by being in unison with nature? Or whether nature is a random agglomeration of substances interacting solely through random physical and chemical processes (2,3).

The recent evolution of aromatherapy as a popular phenomenon, in all its incarnations from the 'French' medical to the British complementary approach has brought these hard questions to the forefront. There is no other field in contemporary healing which integrates such seemingly incompatible concepts. Scientific exploration of essential oil composition and pharmacology - for review and summary see refs (4,5,6,7) - is present in aromatherapy right next to an appreciation of the complex and hard to quantify effects of cultural and cognition mediated effects of fragrance (8). The increasing knowledge about the complexities of the plant organism and the more than surprising ways in which it can interact with human physiology and metabolism lead the unbiased observer to notions of spirituality or wonderment about creation.

Recent advances in the scientific understanding of the multi layered interactions of essential oils with metabolic systems and in receptor science, including a rapidly evolving understanding of the connectedness of the endocrine, nervous and immune systems or in other words of the connections between our physical and psychological and/or emotional well being point to a much broader usefulness of essential oils in the process of preventing and treating disease than science thought possible only ten years ago (9,10).

When investigating pharmacological properties of essential oils or plant extracts authors often state that they were initially following cues provided by traditional or ethnopharmacological uses of such oils or extracts by indigenous peoples around the world. More recently this line of reasoning expanded into taking cues from historic scriptures. Studying historically mentioned uses of plants is indeed fascinating and not surprisingly plants which have enjoyed popularity throughout the times such as Ginger, Frankincense and Myrrh provide ample opportunity to explore a broad spectrum of uses, which, in accordance with the cultures that pioneered these, link the medicinal with the ritual and spiritual (11,12,13). Through the acceptance of the complex effects of these plants questions about the integration of the medicinal with the ritual/religious and the aromatic, find their way back into the introductory chapters of rational scientific studies.

Natural agents interacting with multiple physiological target systems: Myrrh and Ginger

In the past scientific evaluation of the properties of essential oils followed very much the concepts of conventional pharmacology. Direct action of essential oils against fungal, bacterial and viral pathogens, pharmacological assessment of their sedative and spasmolytic effects - among others - as well as their clinical efficacy in relieving the symptoms of autonomic nervous system imbalances have been described in the literature. (4,5) Following, the example of selected substances from the essential oil of Myrrh shall be discussed to illustrate the various interactions one oil or oil component can have with multiple physiological target systems.

Myrrh, in its various incarnations is an aromatic plant on which humans in different cultures have relied for as long as there is recorded history. It is mentioned in humanity's oldest epic, the Gilgamesh from Mesopotamia in which Ut-napitshti, the urfather thanks God for his salvation from the Deluge by burning Cedarwood and Myrrh. It is mentioned in practically every scripture of antiquity including the Egyptian Papyrus Ebers (appr. 1550 BC) as a component of the classic medicine/incense Kyphi, the writings of Hippocrates and Roman authors (at the time Rome imported 600 tons of Myrrh p. a., an amount which even multiplied later under the rule of some of Rome's more lavish and extravagant emperors). For detailed accounts on the use of aromatic plants throughout history see (11,13,14).

Products from resins secreted by different species of Gommiphora shrubs common in Northern Africa, known in Somalia under the name *habik hadi* and in English texts usually called scented Myrrh or bissabol are all (Gommiphora africana, G. mucul, G. guidotti or G. molmol) brought into commerce under the collective name Myrrh.

In North African traditional medicine the resin is used for stomach complaints including diarrhea and topically for treatment of wounds. A remedy is prepared by stirring crushed resin into water. In ancient Egypt it was used for embalming and in Palestine as an anointing oil. In ancient Greece and Rome Myrrh was used as a remedy for skin sores, for treating mouth and eye infections, as a cough remedy, against worm infestation and for cattle abdominal pains. It is mentioned by Alvarez, Christopher Columbus' doctor, en route to America.

In a recent Italian study of the properties of Myrrh Dolara, Monetti, Pieraccini, Romaelli state: "We wanted to clarify the reason for the disappearance of Myrrh from practical medicine and also shed some light on a contradictory report contained in the Gospels. Mark, in fact, mentions that 'vinum murratum', wine with Myrrh, was offered to Jesus before crucifixion (Mark, ch. 15, verses 21 -33). Matthew, at variance, says that Christ was given 'vinum cum felle mixtum', wine mixed with bile, and after having tasted it, did not want to drink it (Matthew, ch. 27, verses 29 - 40). 'Vinum', as the classical Cookbook by Apicius reports, was often intended in Roman times as water based 'potion' of various ingredients and not necessarily wine. According to a modern scholar the offer of the potion to Christ as recalled by Mark alluded to the habit of confraternities of Jerusalem women to administer pain alleviation compounds to the condemned, whereas in Matthew the scene is likely to represent an act of mockery by soldiers in fulfillment of the prophecies of the scriptures about the sufferings of the prophet" (15).

As expected, Myrrh extracts can differ markedly in their chemical composition. Here we shall examine the effects of a selected compound, T-cadinol, to illustrate how a single natural substance interacts with multiple physiological target systems. It serves as an excellent example for the concepts and workings of modern aroma - or essential oil therapy. The properties demonstrated for T-cadinol range from spasmolytic (16) (T-cadinol inhibits spasms caused by a variety of specific and non specific spasmogens), to antibacterial (17) and antidiarrheal (18). The aforementioned Italian study concludes that furaneudesma-1,3-diene and curzarene, through interaction with opioid receptors, have notable analgesic effects.

Research into the mechanism of the antibacterial effects of T-cadinol corroborates that important events mediated by essential oils originate in the cell membrane. It was found that the number of viable cells rapidly decreases when T-cadinol was added to a culture of *Staphylococcus aureus* in which chloramphenicol was already present. This shows that T-cadinol has a bactericidal rather than a bacteriostatic effect, it kills bacteria in which cell division has already been inhibited. This in turn means that reduced bacterial viability by T-cadinol is not a result of interaction with the synthesis of cell wall components or of macro molecules such as DNA, RNA and proteins, which are typical mechanisms of antibiotics such as β -lactams, quinolones, rifamycins and amino glycosides.

Treatment of *S. aureus* with T-cadinol (50 µg/ml) causes disintegration of the bacterial cell envelope and subsequent fatal loss of intracellular components. The effect of T-cadinol can thus be characterized as bacteriolytic. The primary target of this action may either be the cell wall or the cell membrane. However the action of T-cadinol is not restricted solely to the cell wall of the gram-positive *S. aureus*. Fungi, in the described study *T. mentagrophytes*, are also sensitive to T-cadinol. The antimicrobial effect of T-cadinol, like that of many other terpenoids and/or sesquiterpenoids, seems to be caused by damage to the membrane followed by a loss of cell viability and lysis. This hypothesis explains the anti-microbial spectrum of T-cadinol as well as that of other (sesqui)terpenoids by the difference in the chemical composition of the cell membranes of different species. Similar explanations have been proposed for the selective membrane damaging effects of fungicides of the imidazole type. Fungi and many gram-positive bacteria, which are resistant to imidazoles, have few free fatty acids in their membranes (19). An apparent discrepancy between the number of viable cells and the number of lysed cells estimated by electron microscopy 4 h after addition of T-cadinol (50 µg/ml) indicates that the viability was lost prior to lysis, possibly due to interaction with energy metabolism. It appears very likely that topical application of scented Myrrh has a beneficial effect on wounds infected with the common wound pathogen *S. aureus*. The traditional use of scented Myrrh as a remedy for wounds has thus found rational proof.

Explanation for these phenomena has been presented by Knobloch, Weis and Weigand in 1986 (20). The antibacterial effects of terpenoids were found to be caused by their interference with the primary energy metabolism in the cell membrane (21). This interaction with the energy metabolism explains the reduction in growth rate observed for bacteria treated with concentrations of T-cadinol below the threshold of inhibition. The gradual evolution of understanding in the mechanisms of the antimicrobial activity of terpenoid and sesquiterpenoid components also explains a fact well established empirically by individuals employing these substances for infection treatments, namely There is no observable increase of resistance of microorganisms to essential oils. Many common antibiotics, to the contrary, are effective at first and then lose effectiveness as target microorganisms become resistant to even the most forceful antibiotics.

Considerations on how innate wisdom exists without prompting scientific attention are reflected in a study of Mustafa, Srivastava, Jensen on Ginger (22). In their paper they state that in February 1992 the first scientific work on zoopharmacognosy (the selective use of medicinal plants by animals) was reported (23). A study, on the behavior of Tanzanian chimpanzees, indicated that they swallow, without chewing, whole leaves of a plant related to Sunflower, called Asilia. When the leaves showed up intact in the chimpanzees' feces, researchers concluded that the apes were not after the nutritional value of the leaves. It was discovered that Asilia contains an oil containing thiarubine-A, which not only kills certain worms, fungi and viruses, but also eliminates cancer cells in solid tumors commonly found in breasts and lungs. The chimpanzees evidently use Asilia as a preventive rather than a therapeutic measure. Mustafa, Srivastava, and Jensen go on to state that the dietary habits of present day homo sapiens are affected by culture and especially the selection of foods which big businesses provide. In most of the industrialized nations much of the food is processed and packaged before arriving in the consumer's hands and the user is mostly unaware of its beneficial constituents (with the exception of industrially touted components) as well as its detrimental ones.

The authors use the analogy of the chimpanzee eating Asilia leaves to emphasize that humans are either unaware of or are being prevented from the potential benefit from the wide diversity of foods containing preventive and/or ameliorative bioactive components. According to their observations the properties of Ginger, (*Zingiber officinale*) are apparently unknown to 80% of the scientists, although it is being used by almost 40% of the world's population as a condiment in food and a remedy for several diseases.

Recorded history provides clear pointers for the beneficial properties of Ginger which modern day science, for the most part, either ignores for lack of funding or lacks the tools to assess. The Koran states: "And they (believers) will be given to drink there (heaven) of a cup mixed with zanjabil from a fountain called salsabil". The Arabic zanjabil literally means Ginger. In oriental medicine Ginger is used for a plethora of indications, warming the organism and giving zest to all kinds of foods. As is well known, Ginger has been used for thousands of years to treat diseases in the traditional Ayurvedic, Chinese and Unani-Tibb systems of medicine. In Tibb and Ayurvedic systems preventive and ameliorative effects have been attributed to it in a variety of diseases including

rheumatism, nervous diseases, gingivitis, toothache, painful menstruation, asthma, stroke, constipation and diabetes.

The modern pharmacological evaluation of Ginger established that pungent components (non volatile gingerols) inhibit cyclooxygenase and lipoxygenase activity and thereby reduce inflammation and relieve pain in rheumatic disorders and migraine headache. Ginger extract and [6]-shogaol given orally accelerate and given intravenously inhibit gastrointestinal movement. Galantolactone antagonizes 5-HT₃ receptors which may explain the anti emetic and gastrointestinal movement enhancing effects. A variety of other pharmacological properties of Ginger are discussed. They include effects seemingly antagonistic to each other. Closer examination shows that these systems of self regulating multiple effects are the specific mechanisms by which plant organisms exert a sustained beneficial overall effect onto other species. (See lipophilic messenger hypothesis)

Receptorscience and essential oils

Essential oils have enjoyed great scientific interest in the first half of the century. Their potential pharmacological action was seen as equivalent to the conventional drugs of the time. With the rapid expansion of the industrial scientific sector, providing an enormous number of synthetically reproducible drugs to the medical field, natural substances fell out of fashion. To this day the amount of research investigating the physiological properties of essential oils is marginal compared to main stream research. More than 20 years ago the excellent activity of essential oils to correct Autonomic Nervous System (ANS) imbalances (24,25,26) (spasmolytic and sedative properties) as well as their striking efficacy against viral infections was demonstrated clinically (27). In certain cases viruses have been shown to attach to the same receptors as neuro peptides giving rise to the suggestion that depending on how much of a natural peptide for a particular receptor is available to bind, a virus that fits that receptor will have an easier or harder time invading the cell. With essential oils being highly active on and in the membranes it is reasonable to expect similar mechanisms to be behind the antiviral effects of oils.

More recently a number of studies has explored the interaction of essential oils or their components with various receptor systems. Despite its infancy, this research has already

established a broad spectrum of activity which supports many of the traditionally held assumptions of essential oil efficacy. Following are examples of recently published effects of e.o. in various physiological system.

Essential oils and the autonomic nervous system

Elucidating the interaction between essential oils and receptors and transmitters of the autonomic nervous system (ANS) has led to a much improved understanding of the mechanisms of established therapeutic uses of essential oils. Clinical effectiveness of essential oils in the treatment of vegetative imbalances such as cramps, nervousness, anxiety, headaches, migraines heart palpitations heat flashes etc. was demonstrated in double blind studies (24,25,26).

In addition to demonstrating spasmolytic effects with traditional pharmacological models, terpenoid agents have been shown to bind to receptor sites either competing with physiological ligands (such as Acetyl choline) or acting as non competitive antagonists. It is not unusual to see essential oil components antagonize spasms induced by receptor specific agents such as Acetylcholine, but also those induced by non-specific agents like BaCl₂. Clearly physiological events mediated by essential oils or their components often represent a difficult to penetrate mix between specific ligand behavior and as of yet not clearly understood events they cause in the cell membrane.

This situation is illustrated by the above discussed spasmolytic properties of T-cadinol and its ability to inhibit histamine- and carbachol-induced contractions. The compound does not seem to be a specific receptor antagonist to these agents (28). This is supported by the inhibitory effect of T-cadinol on stimulation of the ileum by barium, which does not induce contractions via a receptor mechanism. Instead Ba²⁺ is known as a classical 'non-specific' spasmogen in the guinea-pig ileum. It is commonly assumed to utilize Ca²⁺ channels to enter into the cell membrane and to induce contractions (29). Smooth muscle contraction induced by K⁺ has been shown to result mainly from membrane depolarization and subsequent influx of extra cellular Ca²⁺ (30). These depolarization-induced contractions were also dose-dependently inhibited by T-cadinol. It was further found that the smooth muscle relaxing effect of T-cadinol was more pronounced in

response to Ba^{2+} - and K^{+} -challenge than to those induced by the histamine or carbachol agonists. The authors conclude that the spasmolytic effect of T-cadinol has to be due to interference with a step in the contraction sequence that is common for the four spasmogenes employed, but more crucial to Ba^{2+} and K^{+} . Consequently the calcium antagonistic properties of (+)-T-cadinol and some of its stereoisomers and related terpenes were investigated in both functional and radioligand binding studies, and compared with those of the dihydropyridine calcium antagonist (+)-nimodipine. Again the terpenes relaxed contractions induced by K^{+} more effectively than those induced by typical ligands. It was found that (+)-T-cadinol caused a competitive inhibition in the binding of dihydropyridine. After modifying chemical structures - masking hydroxyl groups - the authors conclude that the potency of these naturally occurring sesquiterpenoids to relax K^{+} -induced contractions was not correlated to their lipophilicity. Instead they suggest that (+)-T-cadinol and related terpenes represent a new chemical class of calcium antagonists, which interact with dihydropyridine binding sites on the voltage-operated calcium channels (31).

Cardamom:

Another essential oil which has been recently investigated for its interaction with various physiological receptor systems is Cardamom (32,33). In Arab countries its seeds are widely used as a spice in food and as a carminative. Its main properties are given in l' aromatherapie exactement as a digestive tonic and stimulant as well as an expectorant with its main indication being intestinal cramps and circulatory complaints originating from vegetative dystony.

Pharmacological and toxicological properties of the whole oil included anti-inflammatory and analgesic activity. Spasmolytic activity, determined on rabbit intestinal tissue, was found to be due to blocking muscarine receptor sites, using acetylcholine as agonist. Addition of the oil to rabbit jejunum in small doses led to contractions, yet larger doses reportedly had a relaxing effect antagonizing challenges by acetylcholine, nicotine and $BaCl_2$.

The authors conclude that stimulant serotonergic and cholinergic mechanisms exist

parallel to local anesthetic action. They explain the induction of the observed phenomena with the presence of different components in the oil mediating the seemingly opposing local anesthetic and serotonergic and/or muscarinic agonistic effects.

It appears, however, that the observed concentration-induced reversal of effects might be better explained by the suggestions of Teuscher et al (see further down) that low essential oil concentrations lead to specific effects and higher concentrations lead to non-specific effects. (For the influence of Cardamom oil on cardiovascular system see 'circulatory')

Tarragon and Phenylpropanoids

Within the empirical body of experience accumulated by essential oil users the marked effects of Tarragon oil and/or Methylchavicol as well as Anise Seed oil and Anethole are well established. According to Franchomme (4) these components cannot unambiguously be qualified as parasympathomimetic, yet that is what they often are successfully applied for. Their reequilibrating effects for sympathotonic individuals is clearly established. Recent data from an investigation of the oil of *Croton zehnerii* and Methylchavicol, its main constituent support these empirical findings. Methylchavicol was found to relax contractions induced by acetylcholine, histamine and K^+ (34).

Other essential oils or components for which ANS relevant interactions have been recently reported include *Satureja obovata* (Savory) (36), *Thymus granatensis*, *Thymus zygis* and *Salvia lavandulifolia*. It was found that the oils and especially their components Thymol, Carvacrol and Caryophyllene have spasmolytic effects acting in a non competitive antagonistic fashion (35). Within the oils of the same plants Myrcene was found to be a competitive agonist and Borneol a partially competitive agonist against acetylcholine (35).

In Aromatherapy Coumarines are classically expected to have rather strong spasmolytic activity. This could be shown for Bergamottine which decreases frequency and force of heart contractions and inhibits Ca^{++} transport (37).

Asarone free Calamus was found to have as good or better spasmolytic activity, antagonizing histamine, as asarone rich Calamus oil (38). The oil of the Indian plant *Zanthoxylum budrugum* was found to antagonize acetylcholine and histamine (39).

In studies directed at finding solutions for Alzheimer's dementia we can observe that researchers again took the approach of looking into traditional remedies for clues, investigating plants reputed in herbal encyclopedias to enhance memory or alleviate mental disorders. Specifically aromatic plants were investigated for cholinergic activities since this transmitter system is implicated in memory and dementia. Crude extracts were applied to human brain homogenates to determine whether any inhibit acetylcholinesterase. Extracts of sage (*Salvia officinalis*) were found to inhibit the enzyme in a concentration dependent manner. None of the known and commercially available chemical constituents of sage oil so far tested (borneol, caffeic acid, camphor, cineole or thujone) inhibited the enzyme, indicating that the active plant constituent(s) may be an as yet unidentified compound(s). (40)

Recent studies reported the effectiveness of *Salvia lavandulifolia* oil and of one of its constituents. The identity of the substance was not disclosed and kept proprietary (41)!

Cholinergic activities often underlie insecticide or vermifuge (antihelminthic) properties of plants. Examining plants for cholinergic receptor interactions it was found that crude alcoholic extracts of Wormwood, Melissa and Angelica displaced nicotine binding to the nicotinic receptor in a concentration dependent manner. Again components of these plants could be relevant in relation to dementia therapy since there is a loss of nicotinic receptors in Alzheimer's disease and related disorders and stimulation of the nicotinic receptor leads to increased receptor numbers.

Metabolic actions of terpenoids: Cancer

In the aromatherapy literature essential oils with high proportions of monoterpene hydrocarbons are generally described as stimulating and invigorating. Lemon and Pine oil are described as detoxifying agents. Valnet calls Pine oil a powerful hepatic antiseptic (42). Recent studies support this notion. Various monoterpene, sesquiterpene hydrocarbon and sesquiterpene alcohol fractions of the oil of *Eucalyptus caleyi* and 15

sesquiterpene alcohols from other Eucalyptus species have been demonstrated to enhance the activity of liver detoxification enzymes. (43).

In a Swedish study of the impact of needle tree terpenes on loggers it was found that terpene exposure lead to increased metabolic activity due to induction of hepatic detoxification enzymes. Also granulocytes exposed to terpenes show increased expression of surface receptors Mac-1 and CR 1, decreased expression of L-selectin. (44)

Studies conducted by Gould and coworkers and other groups with similar focus on the anticarcinogenic properties of monoterpenoids shed an entirely new light on such seemingly innocuous compounds as limonene. In "The chemoprevention of cancer by mevalonate derived constituents of fruits and vegetables" C.E. Elson and S.G Yu (45) demonstrate what common sense and mother's advice has held all along, namely that fruits and vegetables are highly effective in the prevention of (serious) disease. In their words nutritive isoprenoid constituents of fruits, vegetables, cereal grains and essential oils and their components such as limonene, perillyl alcohol or geraniol exhibit a spectrum of anticarcinogenic activities. This ongoing research is probably one of the most outstanding examples in which compounds found in essential oils are associated with the potential prevention and cure of western culture's most feared diseases. It was demonstrated that monoterpenes prevent the carcinogenesis process at both the initiation and progression stages and that they are effective treating early and advanced cancer. Monoterpenes limonene and perillyl alcohol have been shown to prevent mammary, liver, lung and other cancers. In vitro data suggest that they may be effective in treating neuroblastomas and leukemia. Limonene and perillyl alcohol are now evaluated in phase I clinical trials in advanced cancer patients.

The occurrence of a variety of cellular and molecular events associated with dietary intake of these monoterpenes is discussed as underlying their therapeutic effectiveness. In accordance with the aforementioned study terpenes have been found to induce hepatic phase I and II detoxifying enzymes. Monoterpenes have further been shown to inhibit the isoprenylation of small G proteins which could alter signal transduction and result in altered gene expression. Regressing tumors were found to over-express the mannose 6-phosphate/IGF II receptor, which in turn degrades the mammary tumor mitogen IGF II and activates the cytostatic factor TGF- beta. These and other alterations in the gene

expression of mammary carcinomas lead to a G1 cell cycle block, followed by apoptosis, redifferentiation, and finally complete tumor regression in which tumor parenchyma is replaced by stromal elements. It is likely that monoterpenes prevent mammary cancer during their progression stage by mechanisms similar to those that occur during therapy. In contrast, prevention of mammary cancer induced by polycyclic hydrocarbons such as 7,12-dimethylbenzanthracene occur by the induction of detoxifying phase II hepatic enzymes.

There are a variety of mechanisms under discussion all contributing to the anticarcinogenic effects of terpenoids. One which appears highly elegant from the view of aromatherapy involves the interference of plant derived mevalogenins (terpenes) with processes of the mevalogenic pathway in the cell. The growth of chemically initiated and transplanted tumors is suppressed by dietary terpenoids through the inhibition of mevalonate pathway activities. Mevinolin, a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, depletes cells of the intermediate products of the pathway. These intermediates are required for the posttranslational modification of proteins in which the proteins receive lipophilic anchors that bind to membranes. As a consequence of this process being inhibited, nuclear lamins and ras oncoproteins remain in nascent states, and cells do not proliferate. Gamma tocotrienol, perillyl alcohol, geraniol and d-limonene suppress hepatic HMG-CoA reductase activity, which ultimately suggests that the mevalonate pathway of tumor tissues is uniquely sensitive to the inhibitory actions of the dietary terpenoids. (see refs. 46-57)

Anticarcinogenic effects are not limited to limonene and/or terpenoids. Merk, Junginger and Thiele showed that Eugenol and Caryophyllen modified hepatic detoxification processes in specific ways and prevented the formation of polycyclic aromatic hydrocarbons induced carcinomas (58)

Inflammation

During the past few decades, intensive collaborative research in the fields of chronic and acute inflammatory disorders has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. Modern therapeutic approaches are still

not satisfactory and the treatment of inflammatory diseases like rheumatoid arthritis, ulcerative colitis or psoriasis represent unresolved problems (59).

Many factors contribute to the complex course of inflammatory reactions. Microbiological, immunological and toxic agents can initiate the inflammatory response by activating a variety of humoral and cellular mediators. In the early phase of inflammation, excessive amounts of interleukins and lipid-mediators are released and play a crucial role in the pathogenesis of organ dysfunction. Arachidonic acid (AA), the mother substance of the pro-inflammatory eicosanoids, is released from membrane phospholipids in the course of inflammatory activation and is metabolized to prostaglandins and leukotrienes. Various strategies have been evaluated to control the excessive production of lipid mediators on different levels of biochemical pathways, such as inhibition of phospholipase A2, the trigger enzyme for release of AA, blockade of cyclooxygenase and lipoxygenase pathways and the development of receptor antagonists against platelet activating factor and leukotrienes (60).

Some of these agents exert protective effects in different inflammatory disorders such as rheumatoid arthritis or asthma, whereas others fail to do so. Encouraging results have been obtained by dietary supplementation with long chain omega-3 fatty acids like eicosapentaenoic acid (EPA). In states of inflammation, EPA is released to compete with AA inducing the production of less inflammatory and chemotactic derivatives.

While some of aromatherapy's most successful strategies for symptomatic relief of inflammation and trauma the application of essential oils such as *Helichrysum italicum*, *Tanacetum annuum* or *Eucalyptus citriodora* have not found any pronounced scientific interest. Franchomme studied the antiinflammatory effects of common essential oil constituents in models of zymosan opsonized PMNs (61,62) and found p-anisaldehyd, carvacrol and geraniol to be effective antiinflammatory agents.

Sesquiterpene lactones (SLs) have long been known to be pharmacologically highly active. Recently they have been shown to specifically inhibit the transcription factor NF-kappa B (63,64) It could also be shown that SLs prevent the activation of NF-kappa B by different stimuli such as phorbol esters, tumor necrosis factor-alpha, ligation of the T-cell receptor, and hydrogen peroxide in various cell types. Treatment of cells with SLs

prevented the induced degradation of inhibitory proteins I kappa B-alpha and I kappa B-beta by all these stimuli, suggesting that they interfere with a rather common step in the activation of NF-kappa B. (SLs did not interfere with DNA binding activity of activated NF-kappa B nor with the activity of the protein tyrosine kinases p59(fyn) and p60(src). Micromolar amounts of SLs prevented the induced expression of the NF-kappa B target gene intracellular adhesion molecule 1. Inhibition of NF-kappa B by SLs resulted in an enhanced cell killing of murine fibroblast cells by tumor necrosis factor-alpha.

As might have been expected, SLs lacking an exomethylene group in conjugation with the lactone function displayed no inhibitory activity on NF-kappa B.

This transcription factor is one of the key regulators of genes involved in the immune and inflammatory response. It was suggested that inhibition of the transcription factor may present a useful pharmacological target for future treatments of such inflammatory diseases as rheumatoid arthritis and Crohn's disease.

Currently an increasing number of pharmacological assessments of especially sesquiterpenoid compounds come from Brazil. Investigating plant constituents from such plants which are known to be effective in the ethnopharmacologies of the Amazon hold a twofold promise. There is a high likelihood that the traditionally known effects can be demonstrated in a rational scientific way and secondly that such effects might even be tied to this or the unknown novel compound. Sesquiterpenes have been found to be antineoplastic, antiinflammatory antimalarial and antiviral (65,66,67,68). In one example the sesquiterpenoid polygodial inhibits bradykinin and tachykinins mediators of inflammation , activating NK₂ receptors but not NK₁ (69). In other examples alpha Pinene has been shown to have some as of yet not clearly defined antinociceptive effects (70) and linalool was shown to exhibit anticonvulsive properties most likely through interaction with glutamate binding sites 71).

Circulatory conditions

Little is found in the aromatherapy literature on the effectiveness of essential oils for circulatory conditions. 'L'aromatherapie exactement' references Vetiver as an immuno and circulatory stimulant. Recent studies, however, point to some potentially very useful

effects. The generally relaxing effect of Coumarins is reflected in the influence of bergamottine on heart rate (37). It was found to decrease frequency and force of heart contractions. The essential oil of the berries of *Juniperus macropoda* showed CNS depressant activity and it produced a fall in blood pressure without affecting the rate and depth of respiration. A dose-dependent potentiation of the acetylcholine induced contraction of guinea pig ileum and of albino rat uterus was also observed. An evaluation of the composition of this oil should lead to valuable clues on which compound or group of compounds is responsible for lowering blood pressure. It is not unlikely to encounter similar compositions in more readily available or commonly known essential oils.

Cardamom

Intravenous administration of the oil in low concentration induced dose-dependent decreases in the arterial blood pressure and the heart rate. Cardamom oil had an influence on the cardiovascular system (32,33) (investigated through various pharmacological models) but did not depress the isolated perfused rat heart. The depressant effects were significantly antagonized by cyproheptadine but not by mepyramine, ranitidine, hexamethonium, or indomethacin. Atropine only antagonized the induced bradycardia.

Ginger

[6]-Shogaol has been demonstrated to reduce blood pressure by both a central and a peripheral mechanism.

Vetiver

Khusimol, a sesquiterpenoid isolated from the root of *Vetiveria zizanoides*, was found to competitively inhibit the binding of vasopressin to rat liver V1a receptors (72). It appears that this finding about a prominent constituent of Vetiver should stimulate intensified evaluation of this oil among essential oil users, as its non toxic nature and the possibility to apply it in many different ways suggests that reducing this oil to a fixative or base note for fragrance creations does not do justice to its therapeutic potential, which is invoked in 'L'aromatherapie exactement' and finds support with this study.

Sedative effects

The treatment of insomnia and nervousness has been an area in which phytomedicine has been employed quite extensively in the past. Very often quite simple medicaments prove to be effective in treating disturbances in falling asleep or to ensure sleeping all night. Typically plant agents from *Valeriana officinalis*, *Humulus lupulus*, *Melissa officinalis*, *Passiflora*, *Piper methysticum* or *Macropiper latifolium* and *Ammophila arenaria* enjoy great popularity (73). At present thymoleptic, muscle relaxant, motoric sedative and spasmolytic effects of about 70 sedatives derived from plants could be demonstrated in clinical and pharmacological studies.

Valerian

Valerian has been the subject of most scientific investigations concerning the efficacy of phytopharmaceuticals, extracts and/or components of the essential oil for the treatment of nervous conditions and sleeplessness. Subjective improvement in nervous conditions and sleep quality has been established from placebo-controlled double-blind studies. A wide range of pharmacological test methods has been applied to investigate the sedative and tranquilizing effects of different constituents of Valerian and *Nardostachys jatamansi*, but also constituents of other plants.

The methods used for the investigation of *Valeriana officinalis* included the motility reduction of laboratory rodents and the lengthening of thiopental sleep.

Neurophysiological methods included the measurement of the pharmaco-EEG, the desoxyglucose technique measuring the glucosum sediment in different brain structures and the procedure of receptor binding studies for tracing the effective substances. The total extracts of plants have been investigated with positive results in these tests.

Pharmacological studies on individual constituents were performed with valeranone sesquiterpenes, with valerenic acid and related sesquiterpenes, with valepotriates and their degradation products as well as with lignanes. All these substances showed significant but only small effects in various pharmacological models. Therefore, most scientists investigating Valerian favor the opinion that not one single substance is responsible for the efficacy of valerian extract but the cooperation of various

constituents (see refs. 74-81).

What has been outlined here about Valerian holds true also for the oil of *Nardostachys jatamansi*, the composition of which appears to be quite similar to that of *Valeriana officinalis*. It has been suggested that in the past essential oils of *Valeriana officinalis* and *Nardostachys jatamansi* may have been used interchangeably by manufacturers, with *Nardostachys jatamansi*, because of its much lower price, being the stand-in for *Valeriana officinalis*.

Psychosomatic disease

According to Thure v. Uexküll, at least one third but more likely two thirds of all diseases in Western industrialized societies does not have purely physiological causes. Normally the odyssey of pointless surgery and useless therapies lasts up to eleven years before a correct psychosomatic diagnosis is arrived at (82). On the other hand psychosomatic phenomena are often described as autonomic phenomena, which is also incorrect. In every human disease process physiological, psychological and social components interact inseparably and often impenetrably.

In the reality of urban lifestyles so-called negative emotions are repressed more often than not, making them latent stressors during long periods of time. The autonomic nervous system is the platform on which functional disturbances as well as disturbances of organs and organ systems manifest and imprint themselves onto the immune system with far reaching consequences for an individual's state of health or disease (9).

With increasing pervasiveness of modern lifestyles the rise of psychosomatic disease has been dramatic. Before 1950 doctors diagnosed mainly physical ailments in the USA and only 16 - 66 cases per 1000 were considered psychosomatic. After 1950 a drastic increase in psychological disorders to 53 - 333 cases per 1000 inhabitants was observed (83). The same was found true in the UK where psychological disorders doubled between 1955 and 1971. The same change over time was observed in the symptoms diagnosed: cramps and paralysis in the past; fear and depression, pain, exhaustion, allergies and asthma today. Fear syndrome (15%) and depression (5-6%) are considered lifelong disorders today (84).

To approach an understanding of the potential of essential oils to bring relief for psychosomatic aspects of diseases and to prevent immune depression it is useful to employ the concept of a psychosomatic network - emotional expression being tied to a specific flow of peptides in the body - as described by Pert in 'Molecules of Emotion' or Ader, Felten and Cohen in 'Psychoneuroimmunology'. According to these authors the chronic suppression of emotions results in a massive disturbance of the psychosomatic network. Pert states that "All emotions are healthy, because emotions are what unite the mind and the body. Anger, fear, and sadness, the so-called negative emotions, are as healthy as peace, courage, and joy. To repress these emotions and not let them flow freely is to set up a dis-integrity in the system, causing it to act at cross-purposes rather than as a unified whole. The stress this creates, which takes the form of blockages and insufficient flow of peptide signals to maintain function at the cellular level, is what sets up the weakened conditions that can lead to disease. All honest emotions are positive emotions".

It is exactly the complicated nature of the interplay between physiological psychological and social components which has prevented a scientific assessment of the most powerful and beneficial effects of aroma or essential oil therapy. While much attention is being paid to quantifiable effects the intrinsic 'healing' nature of essential oils is based on their isoeffective improvements of physiological and emotional states. The studies reviewed here concern themselves with essential oil interaction with many physiological systems all of which resonate back on an individual's physical health, maybe most importantly their ability to reequilibrate ANS imbalances. But this still does not cover the whole spectrum of 'healing' conveyed by essential oils.

Through their olfactory impact, which may vary in its quality and quantity from individual to individual, essential oils uniquely employ the powers of emotional coloring and memory to bear strongly on existing states of health or disease: Neurons which react to olfactory stimulation are found in a variety of brain regions (85,86,87,88). Olfactory stimuli have quick and direct access to those areas of the brain which control such important aspects of our behavior as hunger, thirst, aggression, sexual responses, and fight or flight. Olfactory stimuli also have the ability to influence and to color our perception of emotions.

Specifics of such actions are usually not known to or assessed by conventional studies, the exception being aromachology (8). However aromachology's exclusive focus on psychological events lacks integration with the mid and long term physiological effects of odor impact. Odor impact can induce recollection and associated events which in turn can trigger modification of the immune response.

This absence of commercial/scientific interest in essential oils is also indirectly the reason that popular exploitation of the benefits of essential oils relies heavily on traditional knowledge. As a matter of fact the above described scenario is the fertile ground on which the popularity of essential oil therapy in the late 20th century has blossomed. There is good reason to hypothesize that essential oils are better suited to address and prevent fallout from psychosomatic phenomena than conventional medicine, whose tools, according to its own admission work best for the treatment of purely physiological diseases. Conventional medicine emphasizes purely symptomatic and physiological aspects, in order to maintain market share for its products and services. This is the reason why patients, whose needs are insufficiently addressed by these products, turn to healing modalities which also respect the nonmaterial aspects of human life.

Contemplating the various therapeutic properties of a single essential oil like Myrrh or a single plant such as Ginger offers an explanation for their popularity in the past as well as one for their current resurgence in popularity. Essential oils can bring relief not only for psychosomatic diseases. This in turn prevents or improves the states of depressed immune response which in turn acts to prevent or improve resulting physiological conditions. In most of these cases essential oils act by interacting with multiple target systems at once, improving emotional well being, thus raising the body's ability to defend itself as well as acting physiologically, for instance by improving immunoglobuline levels or acting directly against pathogens, such as the Herpes Virus. The end result is a wholistic treatment of the Herpes phenomenon, resulting in reduced outbreak frequency and in most cases very quickly in the absence of any novel outbreaks.

Lipophilic messenger hypothesis

From surveying the literature it becomes clear that terpenoid, sesquiterpenoid and phenylpropanoid molecules interact with a large number of human metabolic systems. This would indicate, as outlined in 'Medical Aromatherapy', that various simple and complex organisms have used these molecules during their coevolution to communicate with each other, to influence, repel, deceive the other organisms in ever new and changing ways. Relatively simple aromatic molecules seemingly have played an important role in these exchanges at almost any given time.

From the standpoint of aromatherapy two conclusions appear:

A) Effectiveness and likelihood of interaction of aromatic molecules with various physiological and psychological target systems is not limited to the instances currently described in the literature. Assumption of therapeutic effects based on traditional or ethnopharmacological information is often correct.

B) Recent research shows that specific effects are also being observed frequently and gathering of information based on scientific experimentation would most likely yield surprising results.

From a scientific viewpoint it seems that powerful interactions of terpenoids with components or processes in the cell membrane mediate most of the discussed effects. Precise mechanisms probably vary from substance to substance and more investigations like those on T-cadinol are needed. Already in 1980 Teuscher, Melzig, Villman and Möritz (90) concluded that essential oils exert their effects by interactions with processes in lipophilic areas of cell membranes, endomembrane systems or apolar areas of proteins in the membrane (90). The ability of oils to influence the ion permeability of the cell membrane was stated then and is demonstrated impressively by the reviewed studies. Spasmolytic effects of essential oils are in most cases mediated by their ability to inhibit the influx of Ca^{++} ions. Knobloch was able to demonstrate that essential oil components exert their antibacterial effects by inhibiting cellular respiration processes in the cell membranes of the bacteria. The newer studies support this conclusion.

In addition it becomes clear that terpenoids not only influence processes in the membrane but also play a significant role in processes involving surface proteins such as

influencing the rate of receptor expression (needle tree terpenes and cholinergic European herbs).

Indications that terpenoids selectively interact with the transformation of proteins, inhibiting the formation of lipophilic anchors and thus influencing their ability to bind to membranes or that the mevalonate pathway of tumor cells is subject to inhibition by dietary terpenoids can become a major point of departure for a significantly improved understanding of the biomolecular effects of essential oils.

From a general viewpoint of wholistic healing it appears that essential oil therapy is particularly well poised to come to the rescue for any number of typical modern day psychosomatic diseases with their intimately linked physiological and psychosomatic components. Essential oils are soft equilibrating agents, restoring harmony to a system out of balance.

The conservation throughout evolution of the body's physio-emotional communication system is discussed in 'Molecules of Emotion'. Evolution of this system was not limited to more and more complex eucaryotic organisms in the animal kingdom but includes development and evolution of plants. The interaction of lipophilic, volatile plant substances with receptor systems of other organisms has received almost no attention to date. It can be argued that much of the success of a plant species is a consequence of the effective communication of a plant with other organisms via its lipophilic substances. This includes events concerning the plant directly (defensive against invaders or herbivores etc.) but also the dissemination of airborne transmitter substances to exert influence on other organisms. (see the Evolutionary Significance of Pesto, Schnaubelt, Kurt, 'Medical Aromatherapy').

Plant aromatics extend the range of the human psychosomatic network beyond the intra human communication mediated by transmitters - mainly hormones and neuro peptides to a network of communication which comprises plants and their messengers and other organisms including humans.

During the time that cellular life moved out of the water and conquered land the mevalogenic biosynthetic pathways were firmly in place, as was the eucaryotic ability to

manufacture many different messenger substances of hormonal and peptide character. The extensive literature on the interaction between mevalogenins and insect receptor systems demonstrates that this inter species communication between insects and plants and animals and plants is quite intense (91,92,93).

Considering further, as outlined in the chapter on psychosomatic conditions, that many areas of the human brain have neurons reacting to fragrance stimuli, the immediate influence of plants on human psyche and consequently body via ANS mediation becomes obvious. In order to find therapeutic agents to treat the conditions which arise to a large degree from the stresses of alienation from nature, so common in modern lifestyles, one of the most promising avenues is to return to those plant substances our organisms have been missing. With its integrative approach, revitalizing chemical communication between woman/man and plant, reequilibrating the ANS, which enervates the organs of the immune system, aromatherapy is uniquely suited to restore immunity to human organisms. This is not merely a physiological process but also one of the mind and consciousness. It makes aromatherapy all the more modern.

References

- 1 Lowen, Rebecca S. (1997). *Creating the Cold War University: The Transformation of Stanford*. University of California Press.
- 2 Lee, Paul (1995). A plant is not a factory. In *Proceedings of the 1st Wholistic Scientific Aromatherapy Conference*, Schnaubelt, K. (ed) Pacific Institute of Aromatherapy, San Rafael, 45-62.
- 3 Schnaubelt, K. (ed). (1998). *Proceedings of the Third Wholistic Aromatherapy Conference: Science & Emotion* San Francisco. Pacific Institute of Aromatherapy.
- 4 Franchomme, Pierre, Péroël, Daniel (1990). *L'aromathérapie exactement*. Edition Jollois, Limoges.
- 5 Schnaubelt, Kurt (1997). *Advanced Aromatherapy*. Healing Arts Press, Rochester.
- 6 Schnaubelt, Kurt 1995. In *Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils*, Istanbul, Turkey, Baser, K. H. C. (ed) (1995). *Essential Oils- Viable Wholistic Pharmaceuticals for the Future*. Anadolu University

- Press, Eskisehir, Turkey, 3, 269-281.
- 7 Schnaubelt, Kurt (1999). Medical Aromatherapy. Northatlantic Books.
- 8 Jellinek, J. S. (1994). Aroma-Chology: A Status Review. Perfumer & Flavorist, 195, 25.
- 9 Ader, R., Felten, D. L., Cohen, N. (1991). Psychoneuroimmunology. Academic Press.
- 10 Pert, Candace (1997). Molecules of Emotion. Scribner.
- 11 Ohloff, G. (1992). Irdische Düfte Himmlische Lust: Eine Kulturgeschichte der Duftstoffe. Birkhäuser Verlag.
- 12 Rovesti, Paolo (1995). Auf der Suche nach den verlorenen Düften. Irisiana, München.
- 13 Deininger, Rolf (1995). The Magic World of Essential Oils and Scents: Their Effect on the Psyche. In Proceedings of the 1st Wholistic Scientific Aromatherapy Conference, Schnaubelt, K. (ed). Pacific Institute of Aromatherapy, San Rafael, Gustav Fischer, Stuttgart, 90-113.
- 14 Seitz, Renate (1998). The beginning of aromatherapy. A historical overview. In Proceedings of the Third Wholistic Aromatherapy Conference: Science & Emotion San Francisco, K. Schnaubelt (ed). Pacific Institute of Aromatherapy, 76-84.
- 15 Dolara, P., Monetti, G., Pieraccini, G., Romanelli, N. (1996). Characterization of the action on central Opioid receptors of furaneudesma-1, 3-diene, a sesquiterpene extracted from Myrrh. Phytotherapy Research, 10, 81-83.
- ___ Dolara, P. et al. (1996). Analgesic effects of Myrrh. Nature, 379, 29.
- 16 Zygmunt, P., Claeson, P. (1991). Inhibitory effects of the Sesquiterpene T-Cadinol on contractile responses in the isolated Guinea-pig ileum. Phytotherapy Research, 5, 142-144.
- 17 Claeson, P., Rådström, P., Sköld, O., Nilsson, A., Höglund, S. (1992). Bactericidal effect of thesesquiterpene T-cadinol on Staphylococcus aureus. Phytotherapy Research, 6, 94-98.
- 18 Claeson, P., Samuelsson, G. (1989). Screening of some Somalian medicinal plants for antidiarrhoeal effects in mice. Phytotherapy Research, 3, 180-183.

- 19 Sud, I. J. and Feingold, D. S. (1981). Mechanisms of action of the antimycotic imidazoles. *J. Invest. Dermatol.*, 76, 438-441.
- 20 Knobloch, K., Weis, N., Weigand, H. (1986). Mechanism of antimicrobial activity of essential oils. *Planta Medica*, 52, 556.
- 21 Knobloch, K., Weigand, H., Schwarm, H.-M., Vogenschow, H. (1986). Action of terpenoids on energy metabolism. *Progress in Essential Oil Research*. De Gruyter, Berlin New York, 429-445.
- 22 Mustafa, T., Srivastava, K.C., Jensen, K.B. (1993). Pharmacology of Ginger, *Zingiber officinale*. *J. DRUG DEV.*, 61, 25-39.
- 23 Jerome, R. (1992). *Zoopharmacognosy*. The Sciences, 5-6.
- 24 Hammer, O. (1974). Wirkungsnachweis zur therapeutischen Anwendung von Terpenen. *Folia phytotherapeutica*, 6, 4.
- 25 Büchner, K., Hellings, H., Huber, M., Peukert, E., Späth, L., Deininger, R. (1974). Doppelblindstudie zum Nachweis der therapeutischen Wirkung von Melissengeist bei psychovegetativen Syndromen. *Medizinische Klinik (Urban & Schwarzenberg)*, 69, 1032-1036.
- 26 Lingen, K. H (1974). Über die therapeutische Wirksamkeit von Melissengeist bei psychovegetativen Syndromen. *die heilkunst*, 872, 1-3.
- 27 Lembke, A. und Deininger, R. (1987). Wirkung von Terpenen auf mikroskopische Pilze, Bakterien und Viren. In *Phytotherapie: Grundlagen - Klinik - Praxis* Reuter, H.D. Deininger, R., and Schulz, V. (eds) Hippokrates, Stuttgart, 90-104.
- 28 Andersson, M., Bergendorff, O., Shan, R., Zygmunt, P., Sterner O. (1997). Minor components with smooth muscle relaxing properties from scented Myrrh (*Commiphora guidotti*). *Planta Medica*, 63, 250-254.
- Bagi, M. K., Kakrani, H. K., Kalyai, G. A., Satyanarayana, D., Manvi, F. V. (1985). Preliminary pharmacological studies of essential oil from *Commiphora mukul*. *Fitoterapia*, 4, 245-248.
- Claeson, P., Andersson, R., Samuelsson, G. (1991). T-cadinol: a pharmacologically active constituent of Scented Myrrh: introductory pharmacological characterization and high field proton and carbon 13 NMR data. *Planta Medica*, 57, 352-356.

- 29 Samuelli, F., Bonnabello, A., Grassi, A. (1984). Antagonistic activity of verapamil and diltiazem against different intestinal smooth muscle stimuli. *Arzneimittelforschung/Drug Research*, 34, 181-184.
- 30 Hurwitz, L., McGuffee, L. J., Little, S. A. Blumenberg, H. (1980). Evidence for two distinct types of potassium-activated calcium channels in intestinal smooth muscle. *J. Pharmacol.*, 214, 574-580.
- 31 Zygmunt, P.M.; Larsson, B.; Sterner, O.; Hogestatt, E.D. (1993). Calcium antagonistic properties of the sesquiterpene T-cadinol and related substances: Structure-activity studies. *PHARMACOL. TOXICOL.*, 731, 3-9.
- 32 El Tahir, K. E. H., Shoeb, H., Al-Shora, H. (1997). Exploration of some pharmacological activities of Cardamom seed (*Elettaria cardamomum*) volatile oil. *Saudi Pharmaceutical Journal*, 523, 96-102.
- 33 Al-Zuhair, H., El-Sayeh B., Ameen, H.A., Al-Shoora, H. (1996). Pharmacological studies of Cardamom oil in animals. *Pharmacoloegical Research*, 3412, 79-82.
- 34 Coelho-de-Souza, Andreлина, N., Barata, Ednardo, L., Magalhães, Pedro J. C., Lima, Crystianne C., Leal-Cardoso, J. H. (1997). Effects of the essential oil of *Croton zehntneri*, and its constituent estragole on intestinal smooth muscle. *Phytotherapy Research*, 11, 299-304.
- 35 Cabo, J., Crespo, M.E., Jimenez, J., Zarzuelo, A. (1986). The spasmolytic activity of various aromatic plants from the province of Granada: The activity of the major components of their essential oils. *Plantes medicinales et phytotherapie*, 3, 213-218.
- 36 Cruz T., Cabo, M., M., Jimenez J., Zarzuelo, A. (1990). Composition and pharmacological activity of the essential oil of *Satureja obovata* II. Spasmolytic activity. *Fitoterapia*, 613, 247-251.
- 37 Occhiuto, F., Circosta, C. (1997). Investigations to characterize the antiarrhythmic action of bergamottine, a furocoumarin isolated from bergamot oil. *Phytotherapy Research*, 116, 450-453.
- 38 Keller, K., Odenthal, K. P., Leng-Peschlow, E. (1985). Spasmolytic effect of isoasarone-free *Calamus*. *Planta Medica*.
- 39 Agshikar, N. V., Abraham, G. J. S. (1972). Pharmacology and acute toxicity of essential oil extracted from *Zanthoxylum budrunga*. *Indian J. Med. Res.*, 605, 757-762.

- 40 Perry, N., Court, G., Bidet, N., Court, J., Perry, E., (1996). European herbs with cholinergic activities: Potential in dementia therapy. *International Journal of Geriatric Psychiatry*, 1112, 1063-1069.
- 42 Valnet, Jean (1980). *The Practice of Aromatherapy*. Destiny Books, New York.
- 43 Noble, R. M., Herdlicka, J., Sutherland, M., D., Seawright, A. A. (1982). INDUCTION OF HEPATIC MICROSOMAL OXIDATIVE METABOLISM IN MICE BY ESSENTIAL COMPONENTS FROM SOME EUCALYPTUS-SPP AND QUEENSLAND AUSTRALIA FODDER TREES. *QUEENSL J AGRIC ANIM SCI.*, 391, 9-14.
- 44 Johard, Urban, Eklund, Anders, Hed, Jan, Lundahl, Joachim (1993). Terpenes enhance metabolic activity and alter expression of adhesion molecules (Mac-1 and L-selectin) on human granulocytes. *Inflammation*, 174, 499-509.
- 45 Elson, C. E., Yu, S. G. (1994). The chemoprevention of cancer by mevalonate-derived constituents of fruits and vegetables. *J. NUTR.*, 124, 607-614.
- 46 Crowell, P. L., Gould, M. N. (1994). Chemoprevention of mammary cancer by monoterpenoids. *Crit. Rev. Oncogenesis*, 5, 1-22.
- 47 Crowell, Pamela L., Ayoubi, A. Siar, Burke, Yvette D. (1996). Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer. *Adv. Exp. Med. Biol.*, 401.
- 48 Crowell, Pamela L., Elson, Charles E., Bailey, Howard H., Elegbede, Abiodun, Haag, Jill D., Gould, Michael N. (1994). Human metabolism of the experimental cancer therapeutic agent d-limonene. *Cancer Chemother. Pharmacol.*, 351, 31-37.
- 49 Elegbede, J. A., Elson, C. E., Qureshi, A., Tanner, M. A., Gould, M. N. (1984). Inhibition of DMBA-induced mammary cancer by the monoterpene d-limonene. *Carcinogenesis*, 5, 661-664.
- 50 Elegbede, J. A., Elson, C. E., Tanner, M. A., Qureshi, A., Gould, M. N., (1986). Regression of rat mammary tumors following dietary d-limonene. *J. Natl. Cancer Inst.*, 76, 323-325.
- 51 Gould, M. N. (1995). Prevention and therapy of mammary cancer by monoterpenes. *JOURNAL OF CELLULAR BIOCHEMISTRY. SUPPLEMENT*, 22, 139-44.
- 52 Gould, M. N. (1997). Cancer chemoprevention and therapy by monoterpenes. *Environmental Health Perspectives*, 1054, 977-979.

- 53 Gould, Michael N. (1995). Prevention and therapy of mammary cancer by monoterpenes. *J. Cell. Biochem*, 22, 139-44.
- 54 Homburger, F., Treger, A., Boger, E. (1971). Inhibition of murine subcutaneous and intravenous benzo(rst)pentaphene carcinogenesis by sweet Orange oils and d-limonen. *Oncology*, 25, 1-20.
- 55 Jirtle, Randy L., Haag, Jill D., Ariazi, Eric A., Gould, Michael N. (1993). Increased mannose 6-phosphate/insulin-like growth factor II receptor and transforming growth factor β 1 levels during monoterpene-induced regression of mammary tumors. *Cancer Research*, 53, 3849-3852.
- 56 Maltzman, T. H., Hurt, L. M., Elson, C. E., Tanner, M. A., Gould, M. N. (1989). The prevention of nitromethylurea-induced mammary tumors by d-limonen and Orange oil. *Carcinogenesis*, 10, 781-783.
- 57 McNamee, D. (1993). Limonene trial in cancer. *Lancet*, 342, 801.
- 59 Makrides S. C. (1998). Therapeutic inhibition of the complement system. *Pharmacological Reviews*, 501, 59-87.
- 60 Heller, A., Koch, T., Schmeck, J., Van Ackern, C. (1998). Lipid mediators in inflammatory disorders. *Drugs*, 554, 487-496.
- 61 Franchomme, P. (1997). The role of PMNs in inflammatory states. Second wholistic aromatherapy conference San Francisco.
- 62 Franchomme, P. (1997). The intestinal flora, complete component of the immunity. Second Wholistic Aromatherapy Conference, San Francisco.
- 63 Hehner, S. P., Heinrich M., Bork, P. M., Vogt M., Ratter, F., Lehmann V., Schulze-Osthoff, K., Droge, W., Schmitz, M. L. (1998). Sesquiterpene lactones specifically inhibit activation of NF- kappa B by preventing the degradation of I kappa B-alpha and I kappa B-beta *Journal of Biological Chemistry*, 2733, 1288-1297.
- 64 Bork, P. M., Schmitz, M. L., Kuhnt, M., Escher, C., Heinrich, M. (1997). *FEBS Lett*, 402, 85-90.
- 65 Craveiro, A. A., Andrade, C. H. S., Maros, F. J. A., Alencar, J. W. (1979). ESSENTIAL OILS FROM BRAZILIAN RUTACEAE 1. GENUS PILOCARPUS. *J NAT PROD (LLOYDIA)*, 426, 669-671.
- 66 De Souza, M. M., Kern, P., Floriani, A. E. O., Cechinel-Filho, V. (1998). Analgesic

- properties of a hydroalcoholic extract obtained from *Alternanthera brasiliensis*. *Phytotherapy Research*, 124, 279-281.
- 67 Szallasi, A., Biro, T., Modarres, S., Garlaschelli, L., Petersen, M., Klusch, A., Vidari, G., Jonassohn, M., De Rosa, S., Sterner, O., Blumberg, P. M., Krause, J. E. (1998). Dialdehyde sesquiterpenes and other terpenoids as vanilloids. *European Journal of Pharmacology*, 3561, 81-89.
- 69 El Sayah, M., Cechinel Filho, V., Yunes, R. A.; Pinheir, T. R.; Calixto, J. B. (1998). Action of polygodial, a sesquiterpene isolated from *Drymis winteri*, in the guinea-pig ileum and trachea 'in vitro'. *European Journal of Pharmacology*, 34423, 215-221.
- 70 Santos, F. A., Rao, V. S. N., Silveira, E. R. (1998). Investigations on the antinociceptive effect of *Psidium guajava* leaf essential oil and its major constituents. *Phytotherapy Research*, 12, 24-27.
- 71 Elisabethsky, E. (1997). Anticonvulsant properties of linalool and gamma-decanolactone in mice. *WOCMAP II - Abstracts*, Mendoza, Arg.
- 72 Rao, Renee C., Serradeil-Le Gal, Claudine (1994). Khusimol, a non peptide ligand for vasopressin V1a receptors. *Journal of Natural Products*, 5710, 1329-1335.
- 73 Schimmel, K. (1984). PFLANZLICHE SEDATIVA. *THERAPIEWOCHE*, 34, 4117-4127.
- 74 Haensel, Rudolf, Schulz, Jutta (1981). GABA and other amino acids in Valerian root. *Arch. Pharm.*, 3144, 380-381.
- 75 Hazelhoff, B., Malingre, T. M., Meijer, D. K. F. (1982). ANTI SPASMODIC EFFECTS OF VALERIANA COMPOUNDS AN IN-VIVO AND IN-VITRO STUDY ON THE GUINEA-PIG ILEUM. *ARCH INT PHARMACODYN THER* , 2572, 274-287.
- 76 Santos, M. S., Ferreira, F., Cunha, A., Carvalho, A. P., Ribeiro, C. F., Macedo, T. (1994). Synaptosomal GABA release as influenced by Valerian root extract-involvement of GABA carrier. *Arch. Int. Pharmacodyn.*, 3272, 220-231.
- 77 Cavadas, C., Araujo, I., Cotrim, M. D., Amaral, T., Cunha, A. P. (1995). In vitro study on the interaction of *Valeriana officinalis* L. extracts and their amino acids on GABA receptor in rat brain. *Arzneimittel Forschung*, 457, 753-755.
- 78 Ferreira, F., Santos, M. S., Faro, C., Pires, E., Carvalho, A. P., Macedo, T. (1995). Effects of *Valeriana officinalis* on (3H) GABA. Releas in synaptosomes: further evidence for the involvement of free GABA in the Valerian-induced release. *Rev.*

- Port. Farm., 442, 74-77.
- 79 Schmidt, A. (1996). HPLC determination of gamma-aminobutyric acid GABA in psychotropic medicinal plants. GIT Spez. Chromatogr., 161, 14-15.
- 80 Santos, M. S., Ferreira, F., Faro, C., Pires, E., Carvalho, A. P., Cunha, A. P., Macedo T. (1997). The amount of GABA present in aqueous extracts of Valerian is sufficient to account for (3H) GABA. Planta Medica, 605, 475-476.
- 81 Holzl, J. (1998). BALDRIANWURZEL (Valeriana officinalis). - WIRKSAMES PHARMAKON BEI NERVOSITÄT UND SCHLAFSTÖRUNGEN. Zeitschrift für Phytotherapie, 191, 47-54.
- 82 von Uexküll, Thure (1981). Lehrbuch der Psychosomatischen Medizin. München, Wien, Baltimore.
- 83 Lin, T., Stanley, R. (1962). The scope of epidemiology in psychiatry. World Health Organization. Geneva.
- 84 Paykel, E. S., Priest, R. G. (1992). On behalf of conference participants. recognition and management of depression in general practice: consensus statement. Brit. Med. J., 305, 1198-12-2.
- 85 Van Toller, S., Dodd, G. H. (eds) (1992). Fragrance. The Psychology and Biology of Perfume. Elsevier Science Publishers Ltd. Essex..
- 86 Van Toller, S., Dodd, G.H. (eds) (1988). Perfumery: The Psychology and Biology of Fragrance. Chapman & Hall, London.
- 87 Deininger, Rolf (1998). Kultur und Kult in der Medizin. Gustav Fischer, Stuttgart.
- 88 Kimoto, Mari (1997). Neuron response in the piriform cortex to essential oils and terpenes. Toho Igakkai Zasshi, 4456, 495-511.
- 90 Teuscher, E., Melzig, M., Villmann, E., Möritz, K.U. (1990). Untersuchungen zum Wirkmechanismus ätherischer Öle. Zeitschrift für Phytotherapie, 113, 87-92.
- 91 Dyer, L. J., Seabrook, W. D. (1978). Evidence for the presence of acceptor sites for different terpenes on one receptor cell in male *Monochamus ynotatus*. J. Chem Ecol., 45, 523-529.
- 92 Nilles, George P., Zabik, Matthew J., Connin, Richard V., Schuetz, Robert D. (1976). Synthesis of bioactive compounds. A structure-activity study of aryl terpenes as juvenile hormone mimics. J. Agric. Food Chem., 244, 699-708.

- 93 Osir, Ellie O., Riddiford, Lynn M. (1988). Nuclear binding sites for juvenile hormone and its analogs in the epidermis of the tobacco hornworm. *Journal of Biological Chemistry*, 263:25, 13812-13818.